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REPORT TO THE SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND GOVERNMENT RESEARCH COMMITTEE ON GOVERNMENT OPERATIONS UNITED STATES SENATE

RELEASED

Problems In Regulating Selected Vaccines B-164031(2)

National Institutes of Health
Food and Drug Administration
Department of Health, Education,
and Welfare

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

FEB 7, 1973

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON D C 20548

B-164031(2)

Dear Mr Chairman

Pursuant to your request of June 28, 1971, this is the last in a series of three reports relating to activities of the Food and Drug Administration and of the former Division of Biologics Standards, National Institutes of Health Our first report, entitled "Answers to Questions on the Investigational Use of Isoniazid--A Tuberculosis Control Drug," was issued to you on October 7, 1971 The second report, entitled "Problems Involving the Effectiveness of Vaccines," was issued to you on March 28, 1972

This report concerns (1) the safety and potency of adenovirus and adenovirus-influenza vaccines and (2) the safety of pertussis vaccines As agreed upon with your office, we discussed our report with officials of the Food and Drug Administration and the National Institutes of Health but did not obtain their formal written comments

We will not distribute this report further unless you agree or publicly announce its contents

Sincerely yours,

Elmer B. Staats

Comptroller General
of the United States

The Honorable Abraham A Ribicoff
Chairman, Subcommittee on
Executive Reorganization
and Government Research
Committee on Government Operations
United States Senate

Contents

ABBREVIATIONS

DBS	Division of Biologics Standards
FDA	Food and Drug Administration
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
NIH	National Institutes of Health

COMPTROLLER GENERAL'S REPORT
TO THE SUBCOMMITTEE ON
EXECUTIVE REORGANIZATION AND
GOVERNMENT RESEARCH
COMMITTEE ON GOVERNMENT
OPERATIONS
UNITED STATES SENATE

PROBLEMS IN REGULATING SELECTED VACCINES

National Institutes of Health
Food and Drug Administration
Department of Health, Education, and Welfare B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

The Chairman of the Subcommittee on Executive Reorganization and Government Research, Senate Committee on Government Operations, asked the General Accounting Office (GAO) to review aspects of Federal control over drugs and biological products (vaccines, serums, etc)

This report, the third to be issued to the Chairman, concerns (1) the safety and potency of adenovirus and adenovirus-influenza vaccines and (2) the safety of pertussis vaccines GAO discussed the report with Federal officials who regulate vaccines but did not obtain their formal written comments, as agreed upon with the Chairman's office

Background

The law requires that biological products be licensed by the Secretary of Health, Education, and Welfare before they may be transported interstate

The Division of Biologics Standards (DBS) of the National Institutes of Health (NIH), Department of Health, Education, and Welfare (HEW), regulated biological products through June 30, 1972 Effective July 1, 1972, the Secretary of HEW transferred this responsibility to the Food and Drug Administration.

The Code of Federal Regulations sets forth such requirements as standards of safety, purity, potency, and efficacy that must be met before a product can be licensed Under certain conditions the Secretary of HEW may revoke a license

A manufacturer may not release a licensed product for sale until it has completed tests to determine that the product conforms with applicable standards of safety, purity, and potency

Before a product is released for sale, DBS may require manufacturers to submit samples of production lots and test results DBS reviews test results and may conduct tests in its own laboratories to verify the results DBS then either approves the lots for release or rejects them for reasons of safety, purity, or potency.

FINDINGS AND CONCLUSIONS

Adenovirus and adenovirus-influenza vaccines

The potency requirements were not met for any of three adenovirus vaccine licenses and for one of two adenovirus-influenza vaccine licenses issued by DBS to three manufacturers for producing those vaccines

In support of the four license applications, the three manufacturers submitted potency test results on samples of 23 lots of vaccines The vaccines did not meet the potency requirements in 22 of the samples.

Also test results for 23 of 41 lots of adenovirus vaccines and 24 of the 56 lots of adenovirus-influenza vaccines approved for release by DBS from 1957 to 1964 showed failure to meet the potency requirements (See p 9)

NIH officials provided GAO with information which indicated that, while one lot of adenovirus vaccine did not meet the regulations, it was 90 percent effective (See p 13)

Adenovirus and adenovirus-influenza vaccines not meeting the regulations were licensed and approved for release by DBS because the DBS officials responsible were not adhering to the regulations but were using an informal standard that differed from them significantly (See p 9)

DBS did not approve for release adenovirus vaccines after October 1964 when it notified the manufacturers that certain ingredients in the vaccines caused tumors in hamsters Indications of this problem existed as early as 1960, and between 1960 and 1964 DBS took actions which it believed solved the problem (See p 14.)

GAO found no evidence that when DBS notified the manufacturers that it would not approve any further adenovirus vaccines for release, it considered withdrawing from the market those lots that had already been approved for release or that it tried to determine whether any unused vaccine was still on the market (See p 17)

If sufficient evidence existed for DBS to notify the manufacturers that vaccines containing adenovirus would not be approved for release because of a possible safety problem, the same evidence should have suggested that DBS determine whether any vaccines remained on the market and, if so, have them withdrawn

Although no adenovirus and adenovirus-influenza vaccines have been approved for release since 1964, licenses issued for their production are still outstanding The licenses should be revoked because (1) four of the five licenses were issued on the basis of vaccine samples which did not meet requirements and (2) after the licenses were issued certain vaccine ingredients had been shown to cause tumors in hamsters, thus raising significant questions as to the safety of the vaccine, which still have not been resolved (See p 21)

Pertussis vaccines

GAO found no problems concerning the safety, purity, potency, and efficacy of pertussis vaccines that would require any HEW action However, there was information associating the rare occurrence in humans--about one in every million immunizations--of serious adverse reactions following immunization against whooping cough with pertussis vaccines According to the Public Health Service Advisory Committee on Immunization Practices, serious adverse reactions from pertussis vaccines are fewer than serious adverse effects of the disease when the vaccine was not used (See p 18)

RECOMMENDATIONS OR SUGGESTIONS

HEW should.

--Emphasize to officials who regulate biological products that such products are to be licensed and approved for release solely in accordance with the Code of Federal Regulations

--Revoke the licenses for production of adenovirus vaccines. (See p 21.)

MATTERS FOR CONSIDERATION BY THE SUBCOMMITTEE

The Subcommittee should bring GAO's recommendations to the attention of the Secretary of HEW so that they may be acted upon (See p 21)

CHAPTER 1

INTRODUCTION

On June 28, 1971, the Chairman of the Subcommittee on Executive Reorganization and Government Research, Committee on Government Operations, United States Senate, requested that we review selected activities of the Food and Drug Administration (FDA) and the Division of Biologics Standards (DBS) of the National Institutes of Health (NIH), Department of Health, Education, and Welfare (HEW). We agreed to issue three separate reports. The first was issued October 7, 1971, entitled "Answers to Questions on the Investigational Use of Isoniazid--A Tuberculosis Control Drug." The second, entitled "Problems Involving the Effectiveness of Vaccines," was issued March 28, 1972.

This report concerns (1) the safety and potency of adenovirus and adenovirus-influenza vaccines and (2) the safety of pertussis vaccines.

HEW'S RESPONSIBILITY FOR REGULATION OF BIOLOGICAL PRODUCTS

The Secretary of HEW regulates biological products through two statutes--section 351 of the Public Health Service Act, as amended (42 U.S.C 262), which requires biological products[1] to be safe, pure, and potent, and the Federal Food, Drug, and Cosmetic Act of 1938, as amended (21 U S C 301), which requires that biological products be effective.

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[1] A "biological product" is defined under the Public Health Service Act as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analagous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man."

"Safety" is defined in the Code of Federal Regulations (42 CFR 73) as the relative freedom from harmful effects to recipients. Closely allied to safety is the requirement for "purity"--relative freedom from extraneous matter. "Potency" is the ability to effect a given result, as indicated by laboratory tests or by adequately controlled clinical data obtained through administering the product in the manner intended. In accordance with the Federal Food, Drug, and Cosmetic Act, "effectiveness" of a drug is the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

Through June 30, 1972, the Director of NIH, under authority from the Secretary of HEW regulated biological products and DBS was the NIH entity which carried out this responsibility. Effective July 1, 1972, the Secretary of HEW transferred this responsibility to FDA. This responsibility is now carried out by FDA's newly formed Bureau of Biologics.

Licensing of biological products

Biological products and their manufacturers must be licensed by the Secretary of HEW before the products can be sold in the District of Columbia or transported interstate. Specific licensing requirements are contained in 42 CFR 73.

Before June 1960 manufacturers seeking licenses were required to submit applications, including product samples; descriptions of production methods, specimens of the labels, enclosures, and containers proposed for the products when licensed; and summaries of test results.

After June 1960 the applications had to contain additional information, including data derived from laboratory and clinical studies which demonstrated that the product would meet prescribed standards of safety, purity, and potency. According to DBS, the 1960 regulation change was made to reflect the actual DBS practice and also to make the requirements more specific.

Also, according to HEW, since 1962 DBS had been exercising the authority under the Federal Food, Drug, and Cosmetic Act to require biologics to be effective. In February 1972

the Secretary of HEW formally delegated the authority to DBS for requiring such products to be effective as a condition of licensing.

To insure compliance with the regulations, DBS establishes internal ad hoc committees to review license applications and recommend to its Director those biological products acceptable for licensing. As of May 1972 there were 213 licensed biological products and 238 establishments licensed to manufacture such products.

According to the Code of Federal Regulations, the Secretary of HEW may revoke product licenses when, among other things (1) the manufacturing of a product has been discontinued to an extent that a meaningful inspection cannot be made or (2) the product for which the license has been issued fails to conform to the regulations.

Release of biological products

According to the regulations, a licensed product may not be released by a manufacturer for sale until the manufacturer has completed tests to determine that the product conforms with the standards of safety, purity, and potency. Proof of efficacy is not required for release but must be established before licensing.

DBS may require manufacturers to submit, before a product is released for sale, samples of lots and test results. DBS reviews the test results and may conduct tests in its own laboratories to verify the results. DBS either approves the lots for release or rejects them when deemed necessary for reasons of safety, purity, or potency. DBS required the manufacturers to submit such information for adenovirus vaccines before release. DBS records showing the results of adenovirus and adenovirus-influenza potency tests which DBS may have made could not be located.

Adenovirus and adenovirus-influenza vaccines

Adenovirus is one of many viruses causing upper respiratory disease. There are 28 different adenovirus types, each identified by a separate number.

Adenovirus vaccine was first licensed in 1957 to combat adenovirus types 3, 4, and 7 responsible for acute respiratory infection. Three manufacturers were licensed to produce the vaccine, and DBS approved 41 lots for release from 1957 to 1963. Although DBS approved the last lot of adenovirus vaccine for release in 1963, as of June 30, 1972, two of the three manufacturers were still licensed to produce the vaccine. The other manufacturer voluntarily surrendered its license in 1971.

In 1959 and 1960 two of the three licensed manufacturers obtained licenses to produce combined adenovirus-influenza vaccines, and DBS approved 56 lots of the combined vaccines for release from 1959 to 1964. Although DBS approved the last lot of the combined vaccine for release in 1964, as of June 30, 1972, one manufacturer was still licensed to produce it. The other manufacturer voluntarily surrendered its license in 1970.

Because our report entitled "Problems Involving the Effectiveness of Vaccines" (B-164031(2), March 28, 1972) has already discussed influenza vaccines, we are not including information in this report on the influenza portion of the combined adenovirus-influenza vaccines.

Pertussis vaccines

Pertussis vaccines were first licensed for manufacture in 1914, and at June 30, 1972, 10 establishments were licensed to manufacture products containing pertussis vaccines[1]. From 1966 through 1970, about 107 million doses of products containing pertussis vaccines were distributed in the United States.

These vaccines are used to immunize against whooping cough--a highly communicable respiratory disease occurring mostly in children characterized by a peculiar series of quick short coughs ending in a prolonged whooping respiration. In 1970, 76 percent of U.S. children between the ages of 1 and 4 received pertussis vaccines.

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[1]Pertussis vaccine is usually combined with diphtheria vaccine and tetanus toxoids. The combined product is commonly known as DTP.

CHAPTER 2

LICENSING AND RELEASE OF ADENOVIRUS AND ADENOVIRUS-INFLUENZA VACCINES NOT MEETING POTENCY REQUIREMENTS

Potency requirements set forth in 42 CFR 73 were not met for any of three adenovirus vaccine licenses and for one of two adenovirus-influenza vaccine licenses issued by DBS to three manufacturers for producing those vaccines. In support of the four license applications, the three manufacturers submitted potency test results on samples of 23 (18 adenovirus and five adenovirus-influenza) lots of vaccines. The test results on 22 of the samples showed the vaccines did not meet the potency requirements.

In addition, for 23 of the 41 lots of adenovirus vaccines and 24 of the 56 lots of adenovirus-influenza vaccines which were approved by DBS for release between 1957 and 1964, test results showed failure to meet the potency requirements for release.

The requirements of the Code of Federal Regulations for licensing and releasing adenovirus vaccines require that each lot be subjected to an animal potency test to permit an estimation of the vaccine's strength in relation to a reference vaccine which DBS was to supply to the manufacturers. The regulations require that the average strength for each adenovirus type in the vaccine equal or exceed the corresponding value of the reference vaccine for the lot to be satisfactory for licensing or release.

Adenovirus and adenovirus-influenza vaccines not meeting the regulations were licensed and approved for release by DBS because responsible DBS officials were not adhering to the regulations but were using an informal standard, which differed from them significantly.

LICENSING OF VACCINES

The three manufacturers licensed by DBS for producing adenovirus vaccine submitted samples of six lots each in

support of their applications for licenses and their test results on the six lots.

Of the 18 lots submitted, the potency of 17 lots was less than the reference vaccine and therefore did not meet the potency requirements of the Code of Federal Regulations.

For example, one manufacturer licensed for production of adenovirus vaccines on March 20, 1959, submitted, with his license application, test results on six lots of which five were subpotent. In addition, the manufacturer even noted on the protocols that the five lots were subpotent. A DBS official, who reviewed the protocols, also reported the five lots to be subpotent.

Shown below are the results of the manufacturer's potency tests of the six lots expressed as a percentage of the reference vaccine (the reference vaccine was equal to 100 percent).

	Adenovirus type		
Lot	3	4	7
A	278	81	84
B	113	13	111
C	141	50	81
D	283	33	76
E	252	137	465
F	232	59	343

Even though the manufacturer and a DBS official concluded that five (A, B, C, D, and F) of the six lots were subpotent, the manufacturer was licensed apparently on the basis of the recommendation of an ad hoc committee. In its report dated February 9, 1959, the committee concluded that only lots B and D were of low potency on type 4. These lots had potency values of 13 percent and 33 percent for type 4. In addition, the committee noted that all lots were of satisfactory potency according to DBS tests.

The only lot which met the potency requirements of the Code of Federal Regulations, in our opinion, was lot E since each type of adenovirus in lot E exceeded the reference vaccine.

In addition, none of the test results on the 12 lots submitted by the other two manufacturers met the potency requirements. Licenses for producing adenovirus vaccine were issued on September 23, 1957, and November 3, 1960, to the other two manufacturers. At June 30, 1972, two of the manufacturers were still licensed to produce adenovirus vaccine

The two manufacturers licensed for producing adenovirus-influenza vaccine each submitted samples of five vaccine lots.

None of the five lots submitted by one manufacturer, licensed on November 3, 1960, met the potency requirements. The licensing files contained no comments by the manufacturer, the DBS reviewer, or the ad hoc committee on the manufacturer's potency test results. An ad hoc committee report did state that DBS test results were satisfactory. At June 30, 1972, this manufacturer was still licensed to produce adenovirus-influenza vaccines.

The five lots submitted by the second manufacturer met the potency requirements.

RELEASE OF VACCINES

The Federal Regulations provide that, to be satisfactory for release, each adenovirus type must equal or exceed the corresponding value of the reference vaccine.

We found that, of the 97 lots of adenovirus vaccine--including adenovirus-influenza--approved by DBS for release between 1957 and 1964, the manufacturers' test results showed 47 lots did not meet the potency requirements.

For example, the manufacturer of one lot, which DBS approved for release on November 7, 1960, performed two potency tests on each of the three virus types in the vaccine. The test results for type 4 showed potency values of 97 percent and 75 percent. For type 7 the values were 47 percent and 34 percent. Both test results for type 3 exceeded the potency requirements. We believe that the lot should have been rejected because neither type 4 nor 7 met the requirements of the regulations.

The DBS laboratory operators noted the failure of vaccines to meet potency standards in two instances. Although there are no written instructions relating to the laboratory operators review, according to DBS officials, laboratory operators are to review the information submitted by the manufacturers, perform their own tests on selected lots, and indicate whether the vaccine lots meet the potency requirements.

In one of the two instances the laboratory operator noted that, on the basis of DBS tests, the potency requirements had not been met for types 3 and 7. The manufacturer's tests showed type 3 had an average potency value of 30 percent, type 4 greater than 100 percent, and type 7 of 66 percent. DBS approved release of the vaccine with a qualification that it was intended to meet a specific military need and that a vaccine with types 4 and 7 would meet this need.

INFORMAL STANDARD FOR ADENOVIRUS POTENCY TESTS

Due to problems with the variability of the potency test, according to DBS, adenovirus vaccines were licensed and approved for release by DBS if the test results showed the vaccine was at least 33-1/3 percent as potent as the reference vaccine. The 33-1/3-percent value was based on a similar variation permitted for poliomyelitis vaccine potency because, according to DBS officials, both tests were similar in procedure and variability.

It is significant that the Code of Federal Regulations for potency testing of poliomyelitis vaccine provides that a 66-2/3-percent variation was acceptable for licensing and release of the vaccine but that the regulations applicable to adenovirus vaccine did not permit the vaccine to be released or licensed if the test results showed the vaccine was less than 100 percent of the reference. The poliomyelitis vaccine regulations were issued at least a year before the adenovirus vaccine regulations, and DBS officials were unable to explain why the adenovirus regulations did not provide for such a variation. In addition, they were unable to provide any documentation to show that DBS was licensing

and approving adenovirus vaccines for release on the basis of the 33-1/3-percent potency criteria.

DBS did reject two lots with values less than 33-1/3-percent potency. However, of the 47 lots that were approved for release without meeting the potency requirements, 10 had potency values of less than 33-1/3 percent. For example, a manufacturer submitted a lot for release to DBS for which it had performed two potency tests. The test results for type 7 showed a potency of 13 percent on one test and 8 percent on the second test. DBS approved the lot for release on November 1, 1962.

EFFECTIVENESS OF ADENOVIRUS VACCINES

NIH officials agreed that DBS licensed and approved the release of lots of adenovirus vaccine in violation of the potency requirements of the Code of Federal Regulations. They advised us, however, that adenovirus vaccines were effective and provided us with an effectiveness study published in 1960 and conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board. This study, which used one lot of vaccine, showed that the vaccine was 90 percent effective against adenovirus type 4 infections; types 3 and 7 infections were not prevalent during the study. According to an NIH official, the study showed that type 4 contained in the vaccine was effective even though it did not meet the potency requirements. For the lot used in the study, the manufacturer performed two potency tests on type 4 before release. One test showed a potency value of 33 percent and the second test showed a potency value of 26 percent.

Our conclusions and recommendations on matters in this chapter are contained in chapter 5.

CHAPTER 3

SAFETY OF ADENOVIRUS VACCINES

The kidney cells of monkeys were used to grow adenovirus and poliomyelitis viruses for producing vaccine. DBS did not approve for release adenovirus vaccines after October 14, 1964, because (1) adenovirus type 7 was shown to cause tumors in baby hamsters and (2) adenovirus types 3, 4, and 7 were believed to have hybridized with a virus from the monkey (Simian Virus-40) which also caused tumors in baby hamsters. Indications of a possible safety problem existed as early as 1960, and from 1960 to 1964, DBS took several actions, which it believed solved the problem.

CONTAMINATION IN VACCINES

Information on the possible contamination of adenovirus vaccines with Simian Virus 40 (SV-40) was presented at a June 1960 meeting of the Pan American Health Organization. At this meeting a researcher from the Merck Institute for Therapeutic Research presented a study which showed that the monkey kidney cells used in adenovirus vaccine production were contaminated with SV-40. The researcher concluded, however, that SV-40 appeared to be just one more simian virus found in monkey kidney cells which should be eliminated. Because adenovirus vaccines were subjected to an inactivation (killing) process, DBS believed that the SV-40 in the vaccine was also killed and thus rendered harmless.

Because a number of simian viruses were recovered from monkey kidney cell cultures, DBS undertook research to find out if these monkey kidney cell cultures could induce tumors in hamsters. The results of this study, which was substantially completed late in 1960, showed that 109 of 154 hamsters injected with monkey kidney cells developed tumors; monkey kidney cells were used to grow adenovirus. However, the study concluded that viruses could not be proved to cause the tumors.

CONTAMINATION NOT KILLED

On April 10, 1961, DBS informed vaccine manufacturers that a letter in the March 18, 1961, issue of a British scientific journal strongly suggested that live SV-40 was present in killed poliomyelitis vaccines. According to the letter, this alarming conclusion of live SV-40 in vaccines was somewhat mitigated by the fact that, so far, the virus had caused no apparent harm to recipients.

DBS stated in its April 10, 1961, memorandum that the present safety test was not adequate to detect small amounts of live SV-40. To change this situation, DBS proposed that Cercopithecus monkey cells, instead of the previously used Macaca monkey kidney cells, be used for safety testing of adenovirus and poliomyelitis vaccines.

On May 18, 1961, the Public Health Service Technical Committee on Poliomyelitis Vaccine, composed of NIH and DBS officials and other poliomyelitis experts, reported on the SV-40 problem. The Committee stated that, on the basis of clinical observations and surveillance of the general population receiving poliomyelitis vaccine, it did not attribute untoward effects to live SV-40 and did not visualize withdrawing the vaccine from the market. The committee did recommend, however, that future lots of the vaccine be free of SV-40.

A similar committee was not established to study the SV-40 problem in adenovirus vaccines. However, DBS, in a May 20, 1961, memorandum to vaccine manufacturers, stated that, although the immediate concern with SV-40 related to poliomyelitis vaccines, the same problem applied to adenovirus vaccines. In this memorandum, DBS also provided the manufacturers with the Public Health Service Technical Committee on Poliomyelitis Vaccine report and indicated that future lots of adenovirus vaccines should be free of SV-40.

On July 12, 1961, DBS informed the manufacturers of adenovirus vaccines that, to comply with the regulations, all lots to be released must be (1) tested on Cercopithecus monkey kidney cells and (2) free of live virus.

In January 1962 DBS research indicated that live SV-40 caused tumors in hamsters. This research was a followup to the 1960 study which showed that the monkey kidney cells, used to grow adenovirus, caused tumors when injected into hamsters. The 1960 study, however, was unable to prove whether a virus in the monkey kidney cells caused the tumors. The 1962 study showed that a virus was responsible and that the virus was SV-40. A study, also published in 1962, by researchers from the Merck Institute came to the same conclusions as did the January 1962 DBS study Because of these results, DBS believed that manufacturing procedures should be changed to require the use of vaccine materials which were free of SV-40 at all stages of manufacture

According to DBS, SV-40 was readily removed from poliomyelitis vaccine but this proved to be extremely difficult in the case of adenovirus vaccines. The test change required on July 12, 1961, gave reasonable assurance of freedom from the live SV-40, but the test was performed after manufacturers subjected the vaccine to a "killing" process However, DBS believed that use of SV-40 free materials before inactivation would increase the margin of confidence in vaccine safety because this requirement would eliminate even killed SV-40 from the vaccine.

Therefore, on July 30, 1962, DBS forwarded to HEW's Office of General Counsel a notice of proposed amendment to the adenovirus regulations that was intended to result in a vaccine that was free of killed SV-40. This amendment was published in the Federal Register and was effective March 5, 1963.

RELEASE OF VACCINES DISCONTINUED

Subsequently, it was found that the regulations of March 5, 1963, did not eliminate SV-40 from the vaccine

NIH researchers reported to the National Academy of Sciences, on October 14, 1964, that adenovirus type 7 caused tumors in hamsters. According to this study, the tumors caused by type 7 had characteristics similar to those produced by SV-40.

Two other studies presented to the National Academy of Sciences, on the same date, showed that adenovirus type 7 could hybridize with SV-40 These studies, one by NIH researchers and the other by researchers of the Baylor University College of Medicine, concurred that adenovirus type 7 can induce tumors similar to those induced by SV-40. According to the researchers, these results suggested the incorporation and transmission of a portion of the SV-40 by the adenovirus

On October 14, 1964, DBS informed the manufacturers that it would not approve any further adenovirus vaccines for release because (1) adenovirus type 7 was shown to cause tumors in baby hamsters and (2) adenovirus type 7 and possibly types 3 and 4 were hybridizing with SV-40

We found no evidence that when DBS notified the manufacturers that it would not approve any further adenovirus vaccines for release, it considered withdrawing from the market those lots of vaccines that had already been approved for release or that it tried to determine whether any unused vaccine was still on the market

Our conclusions and recommendations on matters presented in this chapter are contained in chapter 5

CHAPTER 4

SAFETY OF PERTUSSIS VACCINES

The American Medical Association, in its 1971 Drug Evaluations, estimated that adverse reactions from the use of pertussis vaccines occur about once in every million immunizations in the United States. According to the Public Health Service Advisory Committee on Immunization Practices,[1] severe central nervous system reactions, occasionally with permanent injury or death, occur very rarely after administration of pertussis vaccine. According to the Committee, serious adverse reactions from the vaccine are much fewer than similar effects of the disease when the vaccine was not used.

According to officials of DBS and the Center for Disease Control, which coordinates and evaluates a national program for preventing and controlling communicable diseases, there is no generally accepted or definitive evidence that pertussis vaccine does, in fact, cause serious adverse reactions.

Because of possible adverse reactions from pertussis vaccines, DBS requires manufacturers to include a warning of possible adverse reactions in the package circulars. For example one package circular included the following statement.

> "Encephalopathic [degenerative disease of the brain] symptoms occasionally occur in patients with whooping cough and encephalopathy has been reported following the administration of pertussis vaccines. ***
>
> "The occurrence of any type of neurological symptoms or signs following administration of * * * [the vaccine] is an absolute contraindication to further use."

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[1] This committee--composed of persons from the fields of public health, medicine, and research--was established in 1964 by the Surgeon General to develop recommendations for using the principal biological products in the United States.

In addition, DBS researches the possible adverse reactions caused by the vaccine. For example, one research study has as its overall objective the making of the vaccine relatively free from untoward effects. This study is directed to determining the cause of adverse reactions which follow the administration of pertussis vaccine and the separation of the protective substances contained in the vaccine from those causing the adverse reactions.

Our conclusions on the matters in this chapter are contained in chapter 5.

CHAPTER 5

CONCLUSIONS, RECOMMENDATIONS, AND MATTERS FOR SUBCOMMITTEE CONSIDERATION

CONCLUSIONS

For four of the five licenses issued for producing adenovirus and adenovirus-influenza vaccine, the potency requirements of the Code of Federal Regulations were not met. At June 30, 1972, two of the three manufacturers were still licensed to produce adenovirus vaccines and one of two manufacturers was still licensed to produce adenovirus-influenza vaccines.

In addition, 47 of the 97 lots approved by DBS for release did not meet the potency requirements. Approval for release of most of the vaccines not meeting the regulations was attributable, according to DBS officials, to the use of a potency standard allowing the vaccines to be 66-2/3 percent less potent than the regulations required. However, no internal instructions or other documentation supported the use of this standard. In addition, 10 of the 47 lots were approved by DBS for release that did not meet even the lower standard.

NIH supplied us with information to show that type 4 in one lot of adenovirus vaccine not meeting the potency requirements was 90 percent effective. Such data, however, does not relieve DBS of the responsibility for licensing and approving products for release as required by the Code of Federal Regulations.

The last lot of adenovirus vaccine was approved for release by DBS on August 10, 1964. There was no evidence to indicate, however, that, at the time DBS notified the manufacturers on October 14, 1964, that no further adenovirus vaccines would be approved for release, it (1) considered withdrawing from the market those lots that had been approved for release before October 14, 1964, or (2) attempted to determine whether any unused vaccine was still on the market. If sufficient evidence existed for DBS to notify the manufacturers that adenovirus vaccines would not be

approved for release because of a possible safety problem, the same evidence should have suggested that DBS determine if any vaccines remained on the market and, if so, take action to have them withdrawn.

We believe that the licenses issued for producing adenovirus and adenovirus-influenza vaccines should be revoked because (1) four of the five licenses were issued on the basis of vaccine samples which did not meet requirements and (2) after the licenses were issued, certain vaccine ingredients had been shown to cause tumors in hamsters, thus raising significant questions as to the safety of the vaccine, which still have not been resolved.

We found no problems associated with the safety, purity, potency, and efficacy of pertussis vaccines that would require any HEW action.

RECOMMENDATIONS

HEW should

--Emphasize to officials who regulate biological products that such products are to be licensed and approved for release solely in accordance with the Code of Federal Regulations.

--Revoke the licenses for producing adenovirus vaccines.

MATTERS FOR SUBCOMMITTEE CONSIDERATION

The Subcommittee should bring our recommendations to the attention of the Secretary of HEW so that the recommendations may be implemented.

United States Senate
COMMITTEE ON
GOVERNMENT OPERATIONS
SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND
GOVERNMENT RESEARCH
(PURSUANT TO SEC 7 S RES 31 92D CONGRESS)
WASHINGTON D C 20510

June 28, 1971

Honorable Elmer B. Staats
Comptroller General of the
United States
General Accounting Office Building
441 G Street
Washington, D.C. 20548

Dear Elmer.

The Public Health Service Act authorizes the Division of Biologics Standards of the National Institutes of Health to administer the regulation of biologic products. In the performance of this important function the Division must establish and maintain a high level of testing and inspection of production facilities for biologics produced for sale and shipment in interstate commerce. In addition, the Division has the power to take appropriate action to enforce restrictions on interstate shipments on unlicensed or mislabeled products.

During the past month, members of the staff of the Subcommittee on Executive Reorganization and Government Research and representatives of your office have discussed the regulatory activities of the Division. On the basis of these discussions and other Subcommittee information, it is clear that a review by your office of the regulatory responsibilities of the Division, particularly its activities involving influenza, adenovirus, combined influenza-adenovirus and pertussis vaccines is badly needed.

I therefore request that the General Accounting Office undertake such a study immediately and submit a full report to this Subcommittee at the earliest date possible.

In addition, I have attached a list of questions concerning the Isoniazid TB control drug and the Federal Government's procedures for assuring its safe use. I would like a separate report responding to these questions as well.

In view of the present working relationship between our staffs, further details involving this request can be arranged at the staff level.

Sincerely,

Abe Ribicoff
Chairman

Attachments [See GAO note.]

GAO note: The attachments have not been included in this report.

PRINCIPAL OFFICIALS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE RESPONSIBLE FOR ACTIVITIES DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE		
Elliot L. Richardson	June 1970	Present
ASSISTANT SECRETARY (HEALTH AND SCIENTIFIC AFFAIRS)		
Merlin K. DuVal	July 1971	Present
Roger O. Egeberg	July 1969	July 1971
DIRECTOR, NATIONAL INSTITUTES OF HEALTH (note a):		
Robert Q. Marston	Sept. 1968	Present
COMMISSIONER, FOOD AND DRUG ADMINISTRATION (note a):		
Charles C. Edwards	Feb 1970	Present
DIRECTOR, DIVISION OF BIOLOGICS STANDARDS (note a)		
Roderick Murray	Jan. 1956	June 1972
DIRECTOR, BUREAU OF BIOLOGICS (note a)·		
Harry M. Meyer, Jr.	July 1972	Present

[a]Through June 30, 1972, the Director of NIH was responsible for regulating biological products and DBS was the organizational entity within NIH which carried out this responsibility. Effective July 1, 1972, the Secretary of HEW transferred this responsibility to FDA and it is now carried out by the Bureau of Biologics.